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JAMA Surgery | Original Investigation

Use of Machine Learning Consensus Clustering to Identify Distinct Subtypes of Black Kidney Transplant Recipients and Associated Outcomes

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IMPORTANCE Among kidney transplant recipients, Black patients continue to have worse graft function and reduced patient and graft survival. Better understanding of different phenotypes and subgroups of Black kidney transplant recipients may help the transplant community to identify individualized strategies to improve outcomes among these vulnerable groups.

OBJECTIVE To cluster Black kidney transplant recipients in the US using an unsupervised machine learning approach.

DESIGN, SETTING, AND PARTICIPANTS This cohort study performed consensus cluster analysis based on recipient-, donor-, and transplant-related characteristics in Black kidney transplant recipients in the US from January 1, 2015, to December 31, 2019, in the Organ Procurement and Transplantation Network/United Network for Organ Sharing database. Each cluster's key characteristics were identified using the standardized mean difference, and subsequently the posttransplant outcomes were compared among the clusters. Data were analyzed from June 9 to July 17, 2021.

EXPOSURE Machine learning consensus clustering approach.

MAIN OUTCOMES AND MEASURES Death-censored graft failure, patient death within 3 years after kidney transplant, and allograft rejection within 1 year after kidney transplant.

RESULTS Consensus cluster analysis was performed for 22 687 Black kidney transplant recipients (mean [SD] age, 51.4 [12.6] years; 13 635 men [60%]), and 4 distinct clusters that best represented their clinical characteristics were identified. Cluster 1 was characterized by highly sensitized recipients of deceased donor kidney retransplants; cluster 2, by recipients of living donor kidney transplants with no or short prior dialysis; cluster 3, by young recipients with hypertension and without diabetes who received young deceased donor transplants with low kidney donor profile index scores; and cluster 4, by older recipients with diabetes who received kidneys from older donors with high kidney donor profile index scores and extended criteria donors. Cluster 2 had the most favorable outcomes in terms of death-censored graft failure, patient death, and allograft rejection. Compared with cluster 2, all other clusters had a higher risk of death-censored graft failure and death. Higher risk for rejection was found in clusters 1 and 3, but not cluster 4.

CONCLUSIONS AND RELEVANCE In this cohort study using an unsupervised machine learning approach, the identification of clinically distinct clusters among Black kidney transplant recipients underscores the need for individualized care strategies to improve outcomes among vulnerable patient groups.

Invited Commentary

Supplemental content

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Kidney transplant is the optimal treatment for most patients with end-stage kidney disease (ESKD), providing improved survival and quality of life.[1,2] Allograft and patient outcomes in Black recipients are inferior compared with those in White recipients and recipients of other ethnic and racial groups.[3-11] Inferior outcomes have been attributed to a variety of factors, including longer dialysis duration,[12,13] greater variation in human leukocyte antigen (HLA) polymorphisms,[14-16] stronger immune response,[15] increased immunosuppression,[17-19] different pharmacokinetics of immunosuppressive drugs,[20,21] and the apolipoprotein L1 (*APOL1*) gene.[22] In addition to clinical, immunological, metabolic, pharmacologic, and genetic factors,[14-16,20-22] social, educational, and financial factors further influence racial inequities in transplantation.[7,23,24] Attempts to improve outcomes of Black kidney transplant recipients include modifying immunosuppressant regimens, improving access to care, and reducing financial barriers. Despite these efforts, Black kidney transplant recipients experience inferior graft function and reduced patient and graft survival.[3-11,14,24-27]

Advances in machine learning, a subfield of artificial intelligence allowing computer algorithms to automatically learn and perform a task without explicit programming, have been applied to assist clinical decision support tools in solid organ transplantation.[28-32] Machine learning algorithms can be divided into 3 main groups: supervised learning (such as classification and regression), unsupervised learning (such as clustering, association, and dimensionality reduction), and reinforcement learning.[33,34] Unsupervised consensus clustering is a machine learning approach used to identify novel data patterns and distinct subtypes.[33-35] Unsupervised consensus clustering can discover similarities and heterogeneities among data variables and distinguish them into clinically meaningful clusters.[33,34] Recent studies have demonstrated that distinct subtypes identified by a machine learning consensus clustering approach can forecast different clinical outcomes.[36,37] Improved understanding of different phenotypes of Black kidney transplant recipients may help the transplant community identify individualized strategies to improve outcomes among vulnerable patients in this group. In this cohort study, we analyzed the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) database from January 1, 2015, through December 31, 2019, using an unsupervised machine learning clustering approach to identify clinically distinct clusters of Black kidney transplant recipients and assess individual outcomes.

Key Points

Question Can an unsupervised machine learning approach identify clinically distinct clusters of Black kidney transplant recipients in the US with differing posttransplant outcomes?

Findings In this unsupervised machine learning consensus clustering cohort analysis of Organ Procurement and Transplantation Network/United Network for Organ Sharing data, 22 687 Black kidney transplant recipients were categorized into 4 distinct high-stability phenotypes. These subgroups were associated with different clinical outcomes, including mortality, acute rejection, and death-censored graft loss.

Meaning These findings suggest that better understanding of these subgroups can help the transplant community identify individualized strategies to improve outcomes among vulnerable groups.

Methods

Data Source and Study Population

For this cohort study, we analyzed the OPTN/UNOS database; this database contains patient-level data of all US transplant events. We screened all adult patients (aged ≥18 years) with ESKD who received a kidney-only transplant from 2015 to 2019. We included only Black patients in this study. If patients had multiple kidney transplants during the study period, we selected the first kidney transplant for analysis. This study was approved by the Mayo Clinic institutional review board. The UNOS/OPTN data are publicly available and deidentified; therefore, informed consent was not required. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data Collection

We comprehensively extracted clinically pertinent recipient-, donor-, and transplant-related variables from the OPTN/UNOS database based on previous literature for inclusion in cluster analysis.[6] The variables included recipient age, sex, and body mass index; receipt of a kidney retransplant; kidney donor status; dialysis duration; causes of ESKD; comorbidities; panel reactive antibody (PRA) results; serostatus for hepatitis C virus, hepatitis B virus, and HIV; Karnofsky functional performance; income; insurance; citizenship; educational level; serum albumin level; donor age, sex, and race and ethnicity; history of hypertension in the donor; kidney donor profile index (KDPI) score; HLA antigen mismatch; cold ischemia time; machine perfusion of the kidney; delayed graft function; allocation type; Epstein-Barr virus and cytomegalovirus status; and induction and maintenance immunosuppression. All extracted variables had less than 5% missing data (eTable 1 in the Supplement). We imputed missing data through the multivariable imputation by the chained equation method.[38]

Clustering Analysis

We applied unsupervised machine learning by conducting a consensus clustering approach to categorize clinical phenotypes of Black kidney transplant recipients.[39] We used a prespecified subsampling parameter of 80% with 100 iterations. The number of possible clusters (k) was selected to range from 2 to 10 to avoid excessive numbers of clusters that would not be clinically useful. The ideal number of clusters was ascertained by evaluating the cumulative distribution function, consensus matrix heat map, cluster-consensus plots in the within-cluster consensus scores, and proportion of ambiguously clustered pairs.[33,40] The within-cluster consensus score (range, 0-1) is defined as the mean consensus value for all pairs of individuals belonging to the same cluster.[33] A value closer to 1

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indicates better cluster stability. The proportion of ambiguously clustered pairs (range, 0-1) is calculated as the proportion of all sample pairs with consensus values falling within the predetermined boundaries.[40] A value closer to 0 signifies higher cluster stability.[40] We calculated the proportion of ambiguously clustered pairs using 2 criteria: (1) the strict criteria consisting of a predetermined boundary of (0, 1), where a pair of individuals who had a consensus value greater than 0 or less than 1 was considered ambiguously clustered, and (2) the relaxed criteria consisting of a predetermined boundary of (0.1, 0.9), where a pair of individuals who had a consensus value greater than 0.1 or less than 0.9 was considered ambiguously clustered.[40] The detailed consensus cluster algorithms used in this study for reproducibility are provided in eMethods in the Supplement.

Outcomes

Posttransplant outcomes included death-censored graft failure, patient death within 3 years after kidney transplant, and allograft rejection within 1 year after kidney transplant. We defined death-censored graft failure as the need for dialysis or kidney retransplant while censoring patients for death or at the last follow-up date reported to the OPTN/UNOS database. In contrast, when assessing death outcome, we censored patients at the last reported follow-up date.

Statistical Analysis

Data were analyzed from June 9 to July 17, 2021. After an individual Black patient who received a kidney transplant was assigned a cluster using the consensus clustering approach, we subsequently performed analyses to characterize differences among the assigned clusters. We compared baseline characteristics among the assigned clusters using the analysis of variance test or Kruskal-Wallis test, as appropriate, for continuous variables and the χ^2 test for categorical variables. We determined the key characteristics of each cluster using the standardized mean difference between each cluster and the overall cohort (eMethods in the Supplement). We considered characteristics with an absolute standardized mean difference of more than 0.3 as key characteristics for each cluster. We compared posttransplant outcomes, including death-censored graft failure, patient death, and allograft rejection among the assigned clusters. We estimated the probability of death-censored graft failure and patient death after kidney transplant using the Kaplan-Meier method, and we used the log-rank test to compare between assigned clusters. We assessed hazard ratios (HRs) for death-censored graft failure and patient death based on the assigned clusters using Cox proportional hazards analysis. Because the OPTN/UNOS database did not specify the date of allograft rejection, we assessed odds ratios for 1-year allograft rejection based on the assigned clusters using logistic regression analysis. We selected cluster 2 as the reference group for all outcome comparisons because cluster 2 had the most favorable graft and patient survival outcomes. We did not adjust for between-cluster differences in clinical characteristics because we used these characteristics to assign the clusters through an unsupervised consensus clustering approach. We performed all analyses using R, version 4.0.3 (RStudio, Inc). We used the ConsensusClusterPlus package, version 1.46.0 (Bioconductor Open Source Software for Bioinformatics), for consensus clustering analysis and the MICE command in R, version 4.0.3, for multivariable imputation by chained equation.[38] Two-sided $P < .05$ indicated statistical significance.

Results

We identified 81 548 adult kidney transplant recipients from 2015 to 2019 in the US; of these, 22 687 (27.8%) were Black recipients. We performed consensus clustering analysis for these recipients. The mean (SD) age was 51.4 (12.6) years, 13 635 recipients (60%) were men, 9052 (40%) were women, 2413 (11%) underwent kidney retransplants, and 3153 (14%) had living donor kidney transplants (**Table 1**).

The cumulative distribution function plot displays the consensus distributions for each cluster of Black kidney transplant recipients (eFigure 1A in the Supplement), where the curve being flat in the middle of the graph demonstrates the best stability for 4 clusters. The delta area plot, in turn, demonstrates the relative change in area under the cumulative distribution function curve (eFigure 1B in the Supplement). The largest changes in area occurred between $k = 3$ and $k = 5$. Beyond this range, the relative increase in area became significantly smaller. The consensus matrix heat maps (eFigure 1C and eFigures 2-10 in the Supplement) reveal that the machine learning algorithm identified clusters 3 and 4 with clear boundaries, indicating good cluster stability during repeated iterations. Cluster 4 also had the highest mean cluster consensus score (**Figure 1**A), representing high stability of cluster 4. A favorable low proportion of ambiguously clustered pairs for both strict and relaxed criteria was demonstrated in 4 clusters (Figure 1B). Thus, using baseline variables at the time of transplant, the consensus clustering analysis identified 4 clusters that best represented the data pattern of our kidney transplant recipients.

Clinical Characteristics of Each Kidney Transplant Cluster

Among Black recipients, there were 3196 patients (14%) in cluster 1, 3096 patients (14%) in cluster 2, 7678 patients (34%) in cluster 3, and 8717 patients (38%) in cluster 4. Table 1 shows the clinical characteristics of the identified clusters. Patients in these 4 identified clusters had distinct baseline characteristics. **Figure 2** and eTable 2 in the Supplement show the plot of standardized mean difference to visualize the key characteristics for each cluster.

Most patients in cluster 1 had a previous kidney transplant (2178 [68%]), a median PRA of 99% or greater (IQR, 87%-100%), and a non-extended criterion donor (ECD) deceased donor kidney transplant (2919 [91%]). Patients in cluster 1 were more likely to be women (1786 [56%]); to have conditions other than diabetes, glomerular disease, hypertension, and polycystic kidney disease as the causes of ESKD (1500 [47%]); and to have received a nationally allocated kidney with a lower number of HLA antigen mismatches (1290 [40%]).

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Table 1. Clinical Characteristics According to Clusters of Black Kidney Transplant Recipients

Characteristic	Recipient group[a] All (N = 22 687)	Cluster 1 (n = 3196)	Cluster 2 (n = 3096)	Cluster 3 (n = 7678)	Cluster 4 (n = 8717)	*P* value
Recipient age, mean (SD), y	51.4 (12.6)	48.5 (11.8)	48.4 (13.0)	44.4 (11.3)	59.6 (8.7)	<.001
Recipient sex						
Men	13 635 (60)	1410 (44)	1807 (58)	4961 (65)	5457 (63)	<.001
Women	9052 (40)	1786 (56)	1289 (42)	2717 (35)	3260 (37)	
ABO blood group						
A	6452 (28)	861 (27)	899 (29)	2165 (28)	2527 (29)	<.001
B	4334 (19)	539 (17)	723 (23)	1410 (18)	1662 (19)	
AB	1255 (5)	141 (4)	169 (5)	445 (6)	500 (6)	
O	10 646 (47)	1655 (52)	1305 (42)	3658 (48)	4028 (46)	
BMI, mean (SD)	29.3 (5.7)	28.0 (5.6)	29.3 (5.7)	28.6 (5.8)	30.5 (5.3)	<.001
Kidney retransplant	2413 (11)	2178 (68)	112 (4)	58 (1)	65 (1)	<.001
Kidney donor status						
Non-ECD deceased	17 052 (75)	2919 (91)	151 (5)	7580 (99)	6402 (73)	<.001
ECD deceased	2482 (11)	172 (5)	32 (1)	39 (1)	2239 (26)	
Living	3153 (14)	105 (3)	2913 (94)	59 (1)	76 (1)	
Dialysis duration						
Preemptive	1798 (8)	264 (8)	768 (25)	397 (5)	369 (4)	<.001
<1 y	1787 (8)	215 (7)	666 (22)	404 (5)	502 (6)	
1-3 y	4069 (18)	745 (23)	977 (32)	1080 (14)	1267 (15)	
>3 y	15 033 (66)	1972 (62)	685 (22)	5797 (76)	6579 (75)	
Cause of ESKD						
Diabetes	6460 (28)	359 (11)	860 (28)	464 (6)	4777 (55)	<.001
Hypertension	8189 (36)	650 (20)	924 (30)	4107 (53)	2508 (29)	
Glomerular disease	4027 (18)	598 (19)	800 (26)	1974 (26)	655 (7)	
PKD	839 (4)	89 (3)	175 (6)	293 (4)	282 (3)	
Other	3172 (14)	1500 (47)	337 (11)	840 (11)	495 (6)	
Comorbidity						
Diabetes	8253 (36)	770 (24)	1055 (34)	751 (10)	5677 (65)	<.001
Malignant neoplasm	1580 (7)	218 (7)	169 (5)	386 (5)	887 (10)	<.001
Peripheral vascular disease	2119 (9)	216 (7)	228 (7)	388 (5)	1287 (15)	<.001
PRA, median (IQR), %	0 (0-48)	99 (87-100)	0 (0-9)	0 (0-18)	0 (0-17)	<.001
Positive HCV serostatus	1825 (8)	238 (7)	95 (3)	546 (7)	946 (11)	<.001
Positive HBs antigen	340 (1)	41 (1)	42 (1)	139 (2)	118 (1)	.052
Positive HIV serostatus	767 (3)	43 (1)	66 (2)	437 (6)	221 (3)	<.001
Functional status, %						
10-30	50 (0.2)	6 (0.2)	9 (<1)	11 (<1)	24 (<1)	<.001
40-70	11 869 (52)	1660 (52)	1258 (41)	3810 (50)	5141 (59)	
80-100	10 768 (47)	1530 (48)	1829 (59)	3587 (50)	3552 (41)	
Working income	5883 (26)	914 (29)	1428 (46)	2161 (28)	1380 (16)	<.001
Public insurance	18 504 (81)	2591 (81)	1658 (53)	6632 (86)	7623 (87)	<.001
US resident	22 597 (>99)	3187 (>99)	3075 (99)	7644 (>99)	8691 (>99)	.02
≥Undergraduate educational attainment	12 405 (55)	1897 (59)	2108 (68)	3855 (50)	4545 (52)	<.001
Serum albumin level, mean (SD), g/dL	4.0 (0.6)	3.8 (0.6)	3.9 (0.5)	4.1 (0.5)	3.9 (0.5)	<.001
Donor age, mean (SD), y	38.4 (14.8)	34.8 (13.8)	40.9 (12.0)	28.4 (12.4)	47.2 (11.9)	<.001
Donor sex						
Men	13 064 (58)	2010 (63)	1103 (36)	5102 (66)	4849 (56)	<.001
Women	9623 (42)	1186 (37)	1993 (64)	2576 (33)	3823 (44)	
Donor race						
Black	5918 (26)	909 (28)	2005 (65)	1458 (19)	1546 (18)	<.001
Hispanic	2266 (10)	421 (13)	140 (5)	873 (11)	832 (9)	<.001
White	13 784 (61)	1765 (55)	844 (27)	5150 (67)	6025 (69)	<.001
Other[b]	719 (3)	101 (3)	107 (3)	197 (3)	314 (4)	.002
History of hypertension in donor	5477 (24)	654 (20)	137 (4)	780 (10)	3906 (45)	<.001

(continued)

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Table 1. Clinical Characteristics According to Clusters of Black Kidney Transplant Recipients (continued)

Characteristic	Recipient group[a] All (N = 22 687)	Cluster 1 (n = 3196)	Cluster 2 (n = 3096)	Cluster 3 (n = 7678)	Cluster 4 (n = 8717)	*P* value
KDPI						
Living donor	3153 (14)	105 (3)	2913 (94)	59 (1)	76 (1)	<.001
<85%	17 892 (79)	3028 (95)	163 (5)	7563 (99)	7228 (83)	
≥85%	1552 (7)	63 (2)	20 (1)	56 (1)	1413 (16)	
HLA antigen mismatch, median (IQR)						
A	2 (1-2)	1 (1-2)	1 (1-2)	2 (1-2)	2 (1-2)	<.001
B	2 (1-2)	1 (1-2)	1 (1-2)	2 (2-2)	2 (2-2)	<.001
DR	1 (1-2)	1 (0-1)	1 (1-2)	1 (1-2)	1 (1-2)	<.001
ABDR	5 (4-5)	4 (3-4)	4 (3-5)	5 (4-5)	5 (4-5)	<.001
Cold ischemia time, mean (SD), h	15.8 (9.8)	18.7 (8.4)	2.4 (3.3)	16.1 (8.0)	19.3 (9.1)	<.001
Kidney on pump	9496 (42)	1115 (35)	17 (1)	3216 (42)	5148 (59)	<.001
Delay graft function	6720 (30)	972 (30)	123 (4)	1998 (26)	3627 (42)	<.001
Allocation type						
Local	16 718 (74)	1283 (40)	3079 (99)	6310 (82)	6046 (69)	<.001
Regional	2821 (12)	623 (19)	8 (<1)	652 (8)	1538 (18)	
National	3148 (14)	1290 (40)	9 (<1)	716 (9)	1133 (13)	
EBV risk status						
Low	122 (1)	22 (1)	35 (1)	53 (1)	12 (<1)	<.001
Moderate	21 200 (93)	2970 (93)	2888 (93)	7101 (92)	8241 (95)	
High	1365 (6)	204 (6)	173 (5)	524 (7)	464 (5)	
CMV status						
Donor negative/recipient negative	2531 (11)	261 (8)	458 (15)	1031 (13)	781 (9)	<.001
Donor negative/recipient positive	6554 (29)	1002 (31)	794 (26)	2385 (31)	2373 (27)	
Donor positive/recipient positive	10 398 (46)	1569 (49)	1362 (44)	3017 (39)	4450 (51)	
Donor positive/recipient negative	3204 (14)	364 (11)	482 (15)	1245 (16)	1113 (13)	
Induction immunosuppression						
Thymoglobulin	14 376 (63)	2303 (72)	1711 (55)	4879 (63)	5483 (63)	<.001
Alemtuzumab	3792 (17)	465 (15)	662 (21)	1305 (17)	1360 (16)	<.001
Basiliximab	3684 (16)	243 (8)	607 (20)	1176 (15)	1658 (19)	<.001
Other	328 (1)	46 (1)	55 (2)	101 (1)	126 (1)	.35
None	1547 (7)	222 (7)	186 (6)	557 (7)	582 (7)	.12
Maintenance immunosuppression						
Tacrolimus	20 689 (91)	2942 (92)	2824 (91)	7050 (92)	7873 (90)	.002
Cyclosporine	184 (1)	26 (1)	35 (1)	51 (1)	72 (1)	.11
Mycophenolate	20 907 (92)	2952 (92)	2857 (92)	7139 (93)	7959 (91)	.001
Azathioprine	65 (<1)	5 (<1)	13 (<1)	22 (<1)	25 (<1)	.28
mTOR inhibitors	62 (<1)	17 (1)	11 (<1)	19 (<1)	115 (1)	.01
Corticosteroid	16 131 (71)	2598 (81)	1947 (63)	5579 (73)	6007 (69)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); CMV, cytomegalovirus; EBV, Epstein-Barr virus; ECD, extended criteria donor; ESKD, end-stage kidney disease; HBs, hepatitis B surface; HCV, hepatitis C virus; HLA, human leukocyte antigen; KDPI, kidney donor profile index; mTOR, mammalian target of rapamycin; PKD, polycystic kidney disease; PRA, panel reactive antibody.

SI conversion factor: To convert serum albumin to g/L, multiply by 10.

[a] Unless otherwise indicated, data are expressed as number (percentage) of recipients. Percentages have been rounded and may not total 100.

[b] Includes Asian, American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander.

Most patients in cluster 2 received preemptive kidney transplants (768 [25%]) or received dialysis for less than 3 years before kidney transplant (1643 [53%]). They were less sensitized (median PRA, 0% [IQR, 0%-9%]) and had a lower number of HLA antigen mismatches (median, 4 [IQR, 3-5]). Most recipients in cluster 2 received a kidney allograft from a Black (2005 [65%]), female (1993 [64%]), and living (2913 [94%]) donor without hypertension (2959 [95%]). They experienced less cold ischemia time (mean [SD], 2.4 [3.3] hours), a lower proportion of machine-perfused kidney transplants (17 [1%]), and a lower incidence of delayed graft function after kidney transplant (123 [4%]). In addition, patients in cluster 2 were more likely to have attained an undergraduate educational level or higher (2108 [68%]), to have a working income (1428 [46%]), and to have private insurance (1438 [46%]) compared with the other clusters.

Patients in cluster 3 were younger recipients (mean [SD] age, 44.4 [11.3] years). Most recipients did not have diabetes (6927 [90%]) and had hypertension as the primary cause of ESKD (4107 [53%]). Most patients in cluster 3 received dialysis

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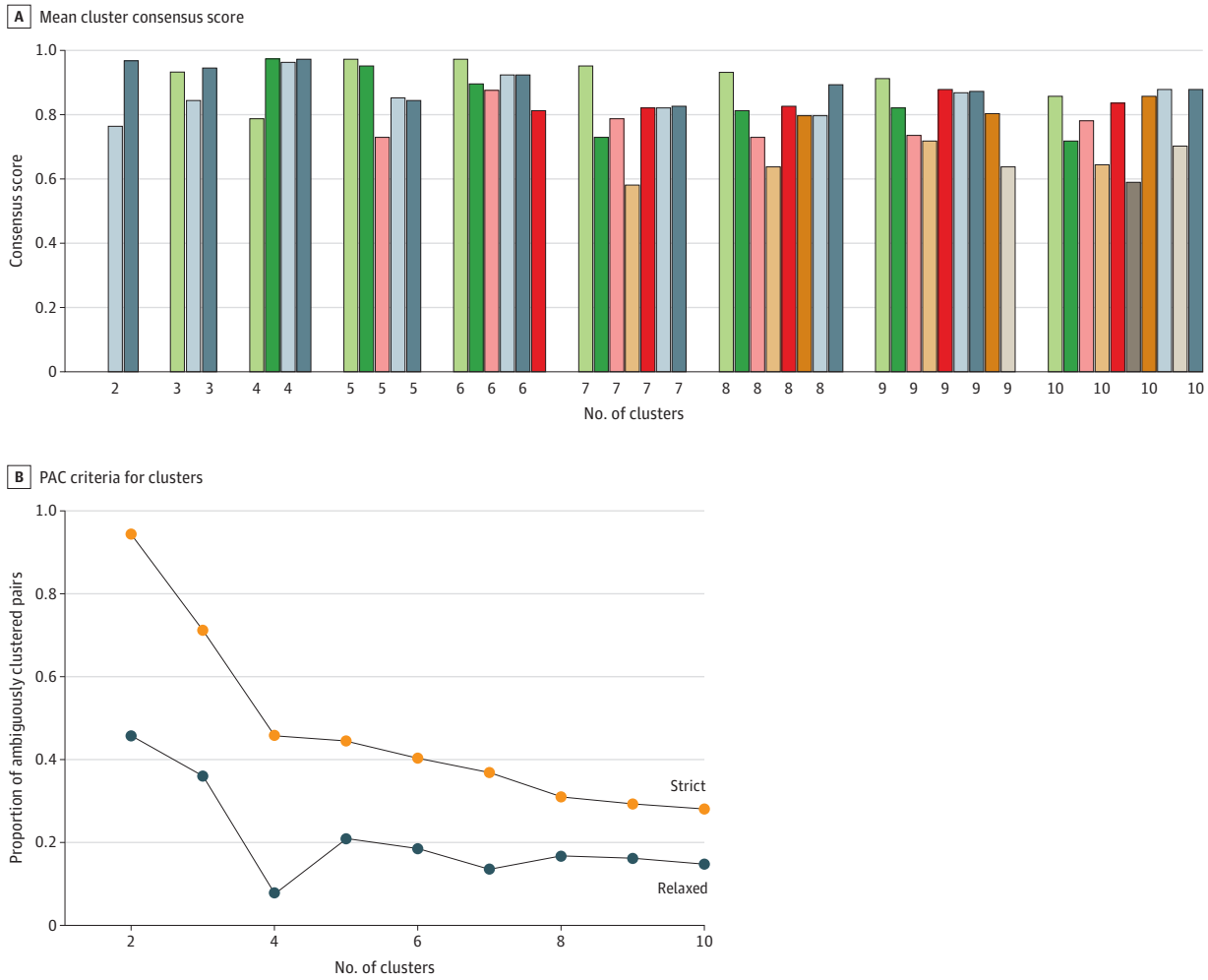
Figure 1. Consensus Clustering Analysis for Data Patterns



A, The bar plot represents the mean consensus score for different numbers of clusters (range, 2-10), representing good cluster stability. B, The proportion of ambiguously clustered pairs (PAC) values assess strict (a pair of individuals who had a consensus value >0 or <1 was considered ambiguously clustered) and relaxed (a pair of individuals who had a consensus value >0.1 or <0.9 was considered ambiguously clustered) criteria for ambiguously clustered pairs.

for longer than 3 years (5797 [76%]). Most received a first-time non-ECD deceased donor kidney transplant (7580 [99%]). Their kidney donors were younger than in the other clusters (mean [SD] age, 28.4 [12.4] years), and most of the donors had a KDPI score less than 85% (7563 [99%]).

Patients in cluster 4 were older recipients (mean [SD] age, 59.6 [8.7] years). This cluster of patients was not sensitized (median PRA, 0% [IQR, 0%-17%]). Most of these patients had diabetes as the cause of their ESKD (4777 [55%]). Although their donors were primarily non-ECD deceased donors (6402 [73%]), they had a higher proportion of ECD deceased donors (2239 [26%]) than other clusters. Their donors were older (mean [SD] age, 47.2 [11.9] years), more likely to have a history of hypertension (3906 [45%]), and had a KDPI score of 85% or higher (1413 [16%]). Kidney transplants for patients in cluster 4 had more cold ischemia time (mean [SD], 19.3 [9.1] hours), greater use of machine perfusion (5148 [59%]), and a higher incidence of delayed graft function (3627 [42%]).

eTable 3 and eFigure 11 in the Supplement showed the proportion of the assigned clusters based on the OPTN regions. Region 5 had the highest proportion of patients in cluster 1 (258 of 1432 [18%]), whereas region 6 had the lowest proportion of patients in cluster 1 (21 of 254 [8%]). Regions 7 and 9 had the highest proportion of patients in cluster 2 (268 of 1437 [19%] and 341 of 1822 [19%], respectively), whereas region 8 had the lowest proportion of patients in cluster 2 (79 of 995 [8%]). Region 8 had the highest proportion of patients in cluster 3 (40 of 995 [40%]), whereas region 9 had the lowest proportion of patients in cluster 3 (505 of 1822 [28%]). Region 11 had the highest proportion of patients in cluster 4 (1599 of 3843 [42%]), whereas regions 4 and 7 had the lowest proportions of patients in cluster 4 (647 of 1846 [35%] and 508 of 1437 [35%], respectively).

Posttransplant Outcomes of Each Kidney Transplant Cluster

Table 2 details cluster-based posttransplant outcomes. The death-censored graft failure at 3 years after kidney transplant

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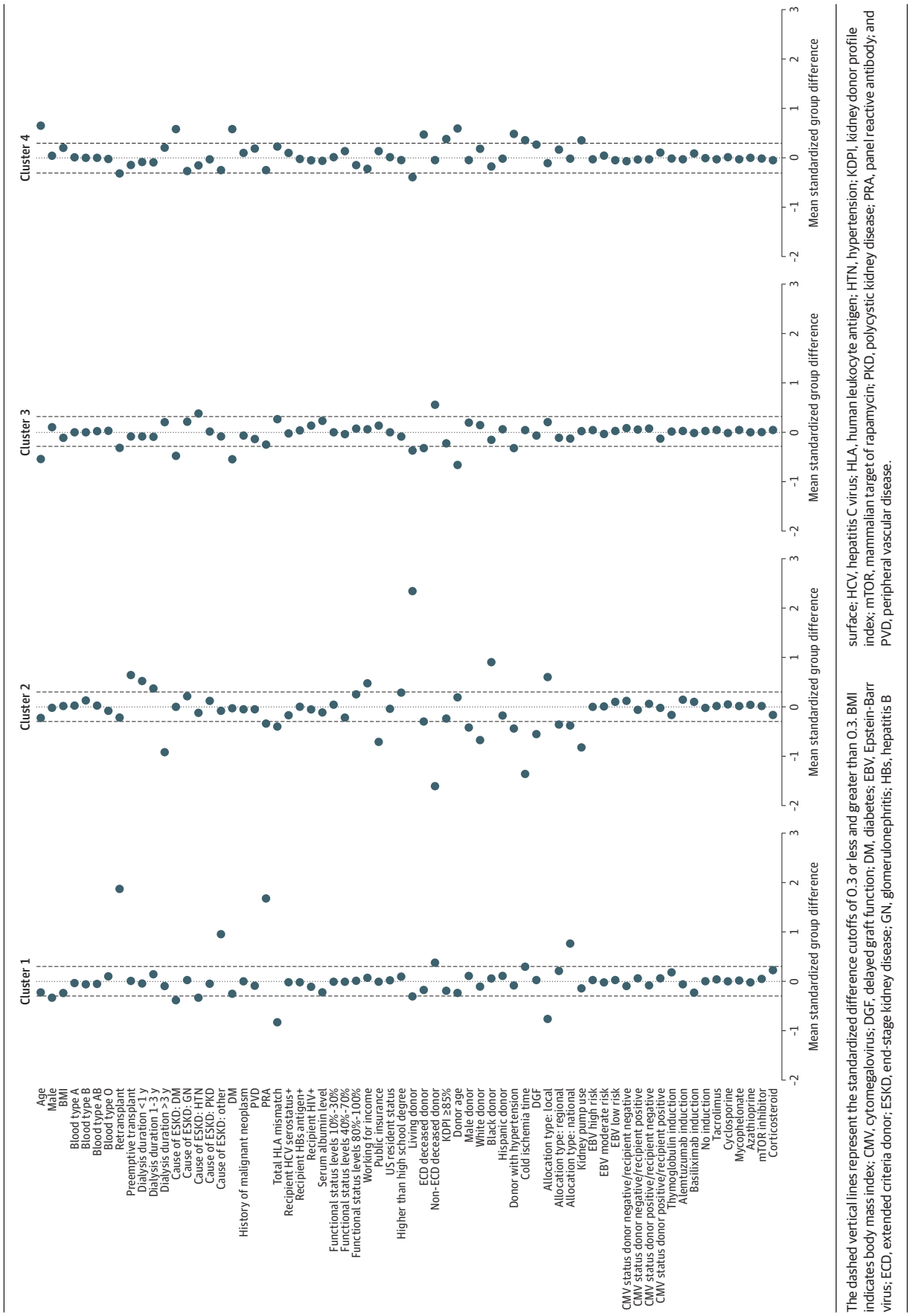
Figure 2. Mean Standardized Differences Across 4 Clusters for Each Baseline Parameter



The dashed vertical lines represent the standardized difference cutoffs of 0.3 or less and greater than 0.3. BMI indicates body mass index; CMV, cytomegalovirus; DGF, delayed graft function; DM, diabetes; EBV, Epstein-Barr virus; ECD, extended criteria donor; ESKD, end-stage kidney disease; GN, glomerulonephritis; HBs, hepatitis B surface; HCV, hepatitis C virus; HLA, human leukocyte antigen; HTN, hypertension; KDPI, kidney donor profile index; mTOR, mammalian target of rapamycin; PKD, polycystic kidney disease; PRA, panel reactive antibody; and PVD, peripheral vascular disease.

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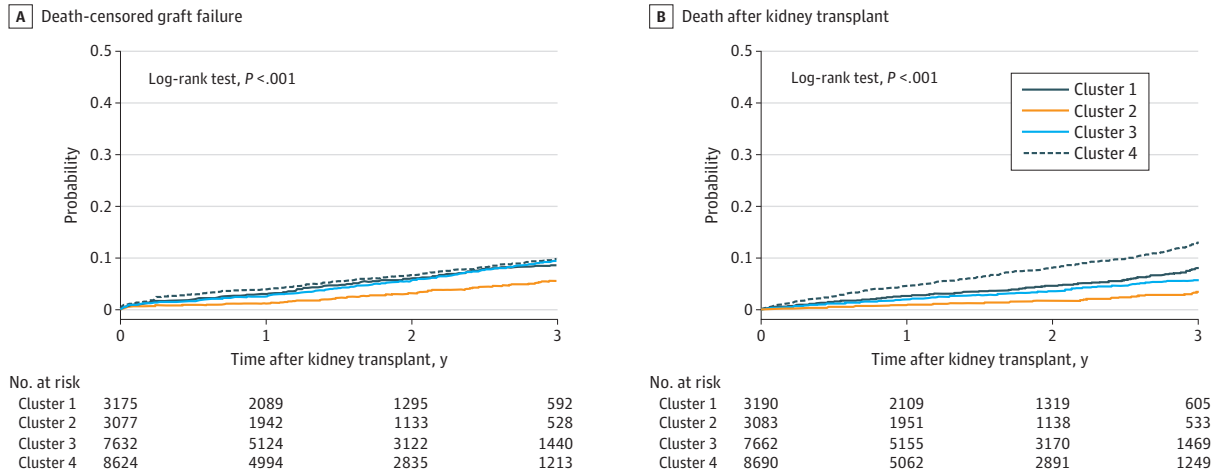
Table 2. Posttransplant Outcomes According to Clusters of Black Kidney Transplant Recipients

Outcome	Cluster 1 (n = 3196)	Cluster 2 (n = 3096)	Cluster 3 (n = 7678)	Cluster 4 (n = 8717)
Death-censored graft loss at 3 y, %[a]	8.7	5.5	9.6	10.2
HR for death-censored graft loss (95% CI)	1.93 (1.49-2.51)	1 [Reference]	1.92 (1.51-2.43)	2.40 (1.91-3.03)
Death at 3 y, %[a]	8.1	3.5	5.8	13.1
HR for death (95% CI)	2.53 (1.84-3.46)	1 [Reference]	1.89 (1.41-2.54)	4.32 (3.26-5.72)
Acute rejection in 1 y, No. (%)	258 (8.1)	147 (4.8)	503 (6.6)	422 (4.8)
OR for acute rejection (95% CI)	1.76 (1.43-2.17)	1 [Reference]	1.41 (1.16-1.70)	1.02 (0.84-1.24)

Abbreviations: HR, hazard ratio; OR, odds ratio.

[a] Estimated from Kaplan-Meier plots (Figure 3).

Figure 3. Kaplan-Meier Plots



Graphs show the estimated probability of death-censored graft failure and patient death after kidney transplant among different clusters of Black kidney transplant recipients. The *P* value was derived from the log-rank test.

was 8.7% in cluster 1, 5.5% in cluster 2, 9.6% in cluster 3, and 10.2% in cluster 4 (**Figure 3**A). Compared with cluster 2, HRs for death-censored graft failure were 1.93 (95% CI, 1.49-2.51) for cluster 1, 1.92 (95% CI, 1.51-2.43) for cluster 3, and 2.40 (95% CI, 1.91-3.03) for cluster 4.

The rate of death at 3 years after kidney transplant was 8.1% in cluster 1, 3.5% in cluster 2, 5.8% in cluster 3, and 13.1% in cluster 4 (Figure 3B). Compared with cluster 2, HRs for death were 2.53 (95% CI, 1.84-3.46) for cluster 1, 1.89 (95% CI, 1.41-2.54) for cluster 3, and 4.32 (95% CI, 3.26-5.72) for cluster 4.

The incidence of allograft rejection within 1 year after kidney transplant was 8.1% in cluster 1, 4.8% in cluster 2, 6.6% in cluster 3, and 4.8% in cluster 4. Clusters 1 and 3 were associated with a higher risk of rejection, with odds ratios of 1.76 (95% CI, 1.43-2.17) and 1.41 (95% CI, 1.16-1.70), respectively. There were no differences in risk of rejection when cluster 2 and cluster 4 were compared.

Discussion

Black recipients of kidney transplants in the US have inferior outcomes. Several variables have been implicated, including higher risk for rejection and socioeconomic factors. These variables are often universally applied to all Black kidney transplant recipients. In this study, an unsupervised machine learning consensus clustering approach was successfully used to categorize Black kidney transplant recipients in the OPTN/UNOS database into 4 distinct phenotypes with high-stability clusters. The characteristics of transplant recipients in these 4 distinct groups include (1) highly sensitized, deceased donor kidney retransplant in cluster 1; (2) preemptive and/or short dialysis time with living donor kidney transplant in cluster 2; (3) younger, with hypertension, and without diabetes receiving low-KDPI kidneys from young deceased donors in cluster 3; and (4) older with diabetes receiving high-KDPI kidneys from ECDs in cluster 4. These distinct subgroups of Black kidney transplant recipients are associated with different clinical outcomes, including mortality, acute rejection, and death-censored graft loss.

Cluster 2 represented the lowest number of Black kidney transplant recipients (3096 [14%]). Patients in this cluster had superior patient survival and the lowest risk for rejection. Most patients in this cluster had preemptive transplants (25%) or had a shorter dialysis duration (53%) and received a living donor kidney transplant (94%). Recipients were less likely to have had a prior transplant or to have diabetes. Compared with other clusters, patients in cluster 2 had excellent functional status,

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were more likely to carry private insurance, and had a higher level of educational attainment. Given these favorable characteristics, patients in cluster 2 demonstrated the best patient and graft survival and had the lowest observed incidence of acute rejection. The excellent outcomes observed in cluster 2 align with known data supporting better and earlier access to health care, preemptive kidney transplant, and improved survival benefits.[7,41-48]

Recipients in cluster 4 were older and more likely to have diabetes and have lower functional status. Cluster 4 represented the largest number of patients (38%). Although this group of recipients was not sensitized (median PRA, 0%) and the risk for rejection was lower (4.8%), most patients received thymoglobulin for induction. Recipients in cluster 4 were more likely to receive ECD kidney transplants and/or have high-KDPI donors with higher cold ischemia times and increased incidence of machine perfusion (59%). Recipients in cluster 4 had the highest rates of delayed graft function (42%) and death-censored graft loss at 3 years (10.2%). In addition to having higher cardiovascular risk, medical comorbidities, and reduced functional status, recipients in cluster 4 also had the lowest number of recipients who worked for income. Given these findings, recipients in cluster 4 may have had increased difficulty with access to posttransplant health care,[26] resulting in increased mortality and graft loss.[5,43,49,50] However, cluster 4 also had lower rates of rejection, likely because of a lower immune response due to being older and having a low PRA.[51,52]

The findings unique to cluster 4 recipients raise opportunities for directed improvements in outcomes. Emphasis on earlier access to transplant, improvements in diabetes care and functional status, and optimization of immunosuppressant regimens are areas of future investigations. Physiological changes associated with senescence can affect drug metabolism and increase the risk of posttransplant infection and malignant neoplasms in older recipients.[52] A recent study using the US National Transplant Registry data (2005-2016)[51] suggested that lower-intensity immunosuppression regimens, such as corticosteroid-sparing treatment, are beneficial for older kidney transplant recipients.[51] Given that patients in cluster 4 had the highest mortality but the lowest rate of acute rejection, future studies are needed to identify whether lower-intensity immunosuppression regimens can reduce posttransplant complications, including infection and cancer,[53-61] and ultimately improve patient survival.

Recipients in cluster 1 were almost exclusively patients with a high PRA (IQR, 87%-100%). More than half of the patients had prior transplants and were women. Recipients in cluster 1 were more likely to receive a kidney from outside the local organ procurement organization (59%), with longer cold ischemia times and higher rates of delayed graft function. Most recipients received thymoglobulin induction along with triple-drug maintenance immunosuppression; however, these patients experienced higher rejection at 1 year and lower allograft survival when compared with recipients in cluster 2. Patients in this cluster had longer dialysis duration and lower functional status compared with recipients in cluster 2. Recipients in cluster 1 had the highest risk for rejection (8.1%). Despite an increased rejection risk, 3-year death-censored graft loss remained superior compared with rates in clusters 3 and 4. Additional strategies for earlier detection of subclinical rejection, including cell-free DNA and access to for-cause and protocol kidney biopsies, may be unique opportunities for improvement in cluster 1.

Recipients in cluster 3 accounted for the second largest group (34%) among these Black kidney transplant recipients. Despite being younger and having fewer comorbidities, including diabetes and peripheral vascular disease, recipients in cluster 3 had a higher risk of mortality when compared with those in cluster 2. Among all clusters, patients in cluster 3 had the highest proportion of patients who received dialysis longer than 3 years (76%). The most common cause of ESKD was hypertension (53%). Most patients received non-ECD deceased donor kidneys with KDPI scores less than 85%. More than half of the donors were young, White male donors from a local organ procurement organization. Although patients in cluster 3 had good functional status, they had lower educational attainment when compared with recipients in cluster 2. Most patients in cluster 3 had public insurance and did not have a working income. In addition to increased mortality risk, patients in cluster 3 also had increased risk of allograft rejection (6.6%) and allograft loss compared with cluster 2. Although these patients were young and nonsensitized and had fewer comorbidities, these patients still had the longest dialysis duration, representing health inequities and disparities in access to kidney transplant among Black patients in the US.[7,23]

Compared with White patients, it is well known that Black patients experienced greater delays in referral to transplant centers, longer waiting times for transplant, and longer duration of dialysis before transplant.[7,12,62-65] Although the 2014 Kidney Allocation System implementation has helped decrease racial disparities in wait-listing, inequalities in wait-listing remain in the US, suggesting the need for additional interventions.[62] Indeed, many factors contribute to racial disparities in kidney transplant, including lower socioeconomic status, limited transplant education, geography, use of the Black race coefficient in estimated glomerular filtration rate formulas, and physician bias.[7,13,26,62] Furthermore, although racial disparities have decreased in deceased donor transplant, ongoing disparities remain in living donor transplant among Black patients.[66]

Limitations

This study has some limitations. We acknowledge that this clustering analysis was based on national registry data. Given the nature of this data source, details regarding factors leading to graft loss, graft rejection, and patient survival are lacking. Because timing of the allograft rejection was not assessed, the rate of allograft rejection might be underestimated owing to the loss to follow-up. To our knowledge, this is the first machine learning clustering approach successfully applied to Black kidney transplant recipients. Through our use of machine learning clustering algorithms, without human intervention or assistance, we identified 4 distinct groups of Black kidney

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transplant recipients. Recipients in cluster 2 had excellent outcomes, which are uncommonly reported for Black patients. For the remaining clusters, the identification of each group's unique variables and susceptibilities allows for improvement in outcomes through individualized medicine. Data reported for Black recipients of kidney transplants are often generalized. The findings of our study illustrate that Black kidney transplant recipients are a heterogeneous population who can be clustered into distinct phenotypes. The findings from our machine learning clustering approach provide increased understanding toward individualized medicine and opportunities to improve care for vulnerable groups of Black kidney transplant recipients. Furthermore, the different cluster distributions among the 11 geographic OPTN/UNOS regions may help identify future strategies for geographical improvement in outcomes for Black kidney transplant recipients.

Conclusions

Inferior outcomes have been described for Black recipients of kidney transplants in the US. Several variables have been implicated for this finding. In this cohort study, an unsupervised machine learning consensus clustering approach categorized Black kidney transplant recipients in the OPTN/UNOS database into 4 distinct phenotypes with high-stability clusters. These distinct subgroups of Black kidney transplant recipients were found to be associated with different clinical outcomes, including mortality, acute rejection, and death-censored graft loss. Better understanding of these Black kidney transplant recipient subgroups may help the transplant community to identify individualized strategies to improve outcomes among vulnerable groups.

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